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1237. Characterization and crystallization of OXA-935, a novel class D OXA-10-like beta-lactamase, found in *Pseudomonas aeruginosa*

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Session: P-72. Resistance Mechanisms

Background. Recently, we described a collection of ST298 *Pseudomonas aeruginosa* (PA) isolates that caused a prolonged epidemic of XDR infections. Many of these contain derivatives of a new plasmid, pPABL048, that harbors an MDR integron, in1697. In1697 contains a series of antimicrobial resistance (AMR) genes, one of which is the class D β-lactamase bla_{OXA-10}. Variants of bla_{OXA-10} have been described that confer both extended-spectrum β-lactamase (ESBL) and carbapenemase activity.

Methods. Of all ST298 isolates, three were resistant to ceftazidime (CTZ). Genomic comparison of in1697 in CTZ-resistant and CTZ-sensitive strains revealed that all three strains harbored a bla_{OXA-10} allele with two single nucleotide variations resulting in amino acid changes at positions 153 (F153S) and 157 (G157D). Using the NCBI database, we identified this allele as unique and defined this β-lactamase as OXA-935. OXA-935 shares the G157D variation with OXA-14 which is known to confer resistance to ceftazidime. We sought to characterize the function of OXA-935 and to determine the crystal structures of OXA-14 and OXA-935.

Results. Deletion of $bla_{OXA-935}$ phenotypically converted all three strains to CTZ-susceptible. Expression of bla_{OXA-14} and $bla_{OXA-935}$ conferred CTZ-resistance to laboratory PA strains PA01 and PA14. Determination of the crystal structures of OXA-14 (PDB code 7L5R) and OXA-935 (PDB code 7L5V) revealed that the F153S variant resulted in increased flexibility in the enzyme's Ω loop. Conformational changes in the Ω loop likely contributed to the lack of carbamylation at lysine-70 (K70) observed in OXA-935. Carbamylation of K70 is known to be critical for enzymatic activity of class D β-lactamases.

Conclusion. OXA-935 is very similar to OXA-14; however, comparison revealed that the F153S variant has unique structural features and is functionally distinct. Despite these differences, both enzymes confer high-level CTZ resistance. As we increasingly rely on β-lactam antimicrobial therapy (e.g. ceftazidime, cefepime) and combination (e.g. ceftazidime-avibactam) therapy to treat MDR PA infections, it is critical that we continue to explore the mechanistic basis of β-lactam AMR in an effort to preserve existing treatments and design novel ones.

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1238. Comparative Activity of Meropenem-Vaborbactam and Ceftazidime-Avibactam Against Multidrug-Resistant *Enterobacter cloacae* from Hospitals in Europe and United States

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Background. *Enterobacter* spp. are part of the ESKAPE pathogens that have been recognized as a threat to human health. Among this genus, *E. cloacae* species complex (ECL) is the most common species that causes human infections. ECL can develop resistance to ß-lactams and other antimicrobial classes due to alterations in gene regulatory pathways. We evaluated the activity of meropenem-vaborbactam, ceftazidime-avibactam, and comparator agents against 235 multidrug resistant (MDR) ECL isolates collected in Europe and the US during 2017-2019.

Methods. A total of 2,459 ECL clinical isolates were collected in 40 European and 33 US hospitals. Isolates were susceptibility tested by reference broth microdilution methods and results were interpreted using CLSI, EUCAST, and US FDA breakpoints. MDR was defined as resistant to 3 or more drug classes when applying the CLSI breakpoints.

Results. MDR ECL were observed among 9.6% of the overall isolates. The MDR rate in Europe (12.0%; 155/1,295) was considerably higher than in the US (6.9%; 80/1,164). Meropenem-vaborbactam inhibited 94.5% and 97.4% of the MDR ECL isolates applying CLSI and EUCAST breakpoints, respectively (Table). Meropenem inhibited 77.9%/85.5% of the isolates (CLSI/EUCAST breakpoints). Cefepime inhibited only 26.0%/16.2% of the MDR ECL isolates while piperacillin-tazobactam inhibited only 13.2%/6.4%. Ceftazidime-avibactam inhibited 93.6% of the MDR ECL isolates. Amikacin and tigecycline were the most active non-beta-lactam comparators, inhibiting 91.9% and 80.0% of these isolates using CLSI/US FDA breakpoints. A total of 93.1% of the isolates were intermediate to colistin applying CLSI breakpoints or susceptible using the EUCAST criteria. Meropenem-vaborbactam inhibited 73.5% and 87.8% of the MDR ECL isolates nonsusceptible to meropenem and cefepime, the main therapeutic option against ECL isolates. Ceftazidime-avibactam inhibited 73.5% of these isolates.

Conclusion. In a global surveillance, ECL is the second most common *Enterobacterales* species/species complex displaying MDR and carbapenem-resistance phenotypes, behind only *Klebsiella pneumoniae*. Meropenem-vaborbactam and ceftazidime-avibactam can be important options to treat infections caused by MDR ECL.

Table. Susceptibility rates for MDR *E. cloacae* species complex isolates

Antimicrobial agent	MDR *E. cloacae* (235 isolates)		Meropenem nonsusceptible and cefepime nonsusceptible MDR *E. cloacae* (49 isolates)	
	%S CLSI[a]	%S EUCAST[a]	%S CLSI[a]	%S EUCAST[a]
Meropenem-vaborbactam	94.5	97.4	73.5	87.8
Ceftazidime-avibactam	93.6	93.6	73.5	73.5
Meropenem	77.9	85.5	0	32.7
Cefepime	26.0	16.2	0	0
Ceftazidime	2.6	0.9	0	0
Piperacillin-tazobactam	13.2	6.4	0	0
Colistin	[93.1][b]	93.1	[91.8][b]	91.8
Tetracycline	25.1	-[c]	36.7	-[c]
Tigecycline	80.0[d]	-[c]	85.7[d]	-[c]
Amikacin	91.9	84.7	83.7	71.4
Gentamicin	42.3	39.3	40.8	32.7
Levofloxacin	17.2	17.2	22.4	22.4

[a]Criteria as published by CLSI (2021) and EUCAST (2021).

[b]Percentage intermediate (no susceptibility breakpoint available).

[c]Breakpoint not available.

[d]US FDA breakpoint applied.

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